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Relationship Among Menopause and Diagnosis Age, Tumor Grade and Subtype, and Prevalence of ABO Blood Groups in Early-stage Endometrial Cancer

Erken Evre Endometrial Kanserde Menopoz ve Tanı Yaşı, Tümör Derecesi ve Alt Tipi ve ABO Kan Gruplarının Prevalansı Arasındaki İlişki

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ABSTRACT

Background: Endometrial cancer (EC) is one of the most commonly diagnosed cancers, particularly in patients aged 60-70 years. Several studies have explored the potential of ABO blood groups as markers for early detection of different types of cancers; however, no conclusive study has been conducted for evaluating the effectiveness of ABO blood groups in early detection of EC. To determine the prevalence of the ABO blood groups in patients with EC, examine whether certain blood groups are highly associated with early-stage EC, and investigate the relationship between the ABO blood groups and clinical and pathological prognostic parameters in patients with EC.

Materials and Methods: The prevalence of ABO blood groups in patients who were operated between 2010 and 2020 and diagnosed with atypical endometrial hyperplasia and non-metastatic, International Federation of Gynecology and Obstetrics early stage (I and II) EC was investigated.

Results: The blood group distribution of 575 patients in the study population was found to be A>O>B>AB, in order of frequency. The blood groups B, A, and AB were the most frequently found in women with atypical endometrial hyperplasia, endometrioid adenocarcinoma or uterine sarcoma, and non-endometrioid adenocarcinoma, respectively (p>0.05). The blood groups A, O, and B were the most common in grades 1, 2, and 3 EC tumors, respectively. Although the age of patients at menopause and diagnosis was found to be lower in those with the blood group AB than in the patients with other blood groups, no significant difference was found among the blood groups in terms of the mean age at diagnosis and menopause (p>0.05).

Conclusion: The results indicate that blood groups have no diagnostic value in the early detection of EC, and hence, cannot be used to predict the risk of EC subtypes, tumor grade, or menopause age.

Keywords: ABO blood group, age at menopause, early stage, endometrial cancer (EC)

ÖZ

Amaç: Endometrial kanser (EK), özellikle 60-70 yaş arası hastalarda en sık teşhis edilen kanserlerden biridir. Çeşitli araştırmalar, ABO kan gruplarının farklı kanser türlerinin erken teşhisi için belirteç olarak potansiyelini araştırmıştır; ancak EK'nin erken saptanmasında ABO kan gruplarının etkinliğini değerlendirmek için kesin bir çalışma yapılmamıştır. EK'li hastalarda ABO kan gruplarının prevalansını belirlemek, belirli kan gruplarının erken evre EK ile yüksek oranda ilişkili olup olmadığını incelemek ve EK'li hastalarda ABO kan grupları ile klinik ve patolojik prognostik parametreler arasındaki ilişkiyi araştırmak amaçlanmıştır.

Gereç ve Yöntemler: 2010-2020 yılları arasında opere edilen, atipik endometriyal hiperplazi ve non-metastatic, Uluslararası Jinekoloji ve Obstetrik Federasyonu erken evre (I ve II) EK tanısı alan hastalarda ABO kan gruplarının prevalansı incelendi.

Bulgular: Çalışma popülasyonundaki 575 hastanın kan grubu dağılımı sıklık sırasına göre A>O>B>AB olarak bulundu. Atipili endometrial hiperplazisi olan kadınların çoğunda B kan grubu, endometrioid adenokanser veya uterin sarkom tespit edilen kadınların çoğunda A kan grubu, non-endometrioid adenokanseri olan kadınların çoğunda AB kan grubu tespit edilmiştir (p>0,05). Grade 1 olanlarda yine, en sık A kan grubu, grade 2'de O ve grade 3 olanlarda en sık B kan grubu izlenmiştir. Kan grubu AB olanların menopoz ve tanı anındaki yaşı daha düşük bulunmuşken (p>0,05), kan grupları arasında tanı anındaki yaş ve menopoz yaşı ortalamaları anlamlı bulunmamıştır.

Sonuç: Bulgular, kan gruplarının EK erken dönem tespitine yardımcı olamayacağını göstermektedir. Belirli bir kan grubunun EK alt tipleri riskini artırdığı, tümör derecesini veya menopoz yaşını etkilediği söylenemez.

Anahtar Kelimeler: ABO kan grubu, menopoz yaşı, erken evre, endometrial kanser (EK)

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Introduction

Endometrial cancer (EC) is the fourth most common cancer in the United States (1) and the most common cancer in developed countries. EC is one of the first five cancers diagnosed in women in Türkiye and the most common type of gynecological cancer. Approximately 3.850 new cases are reported each year in Türkiye. Most patients can be diagnosed at an early-stage (approximately 80% in stage 1). The median age at diagnosis is 63 years (2). Early-stage EC is restricted to the uterus and includes stage 1 and 2 patients (3). The incidence rate of EC peaks between 60 and 70 years of age, and only 2-5% of cases occur before the age of 40 years (1). Chronic anovulation and/or obesity in women under 50 years of age are predisposing to the development of EC (4). Early menarche is a risk factor for EC; conversely, late menopause is less consistently associated with an increased EC risk.

Menopause is a process involving changes in the menstrual patterns over months and years, and is defined as the permanent discontinuation of menstrual periods without any obvious pathological or physiological cause after experiencing amenorrhea for 12 months. The mean age of menopause has been reported to be 51 years worldwide (95% confidence interval between 45 and 55 years), 46-48 years in Türkiye (5).

Blood group antigens are secreted from erythrocytes and epithelial cell surfaces. The H antigen (precursor of A and B antigens) is frequently detected in patients with EC. This explains the increased risk of EC in individuals with non-O blood groups. In the limited number of studies conducted till date, a significant association between the blood group A and uterine cancer has been suggested (6,7).

The role of ABO and Rhesus (Rh) blood groups in oncology has been investigated by various researchers. Following the discovery of blood groups by Karl Landsteiner in 1901 and the discovery that the blood group A plays a role in gastric cancer by Aird in 1953, the role of blood groups in numerous cancer types have been investigated (7).

A study has suggested that human blood group antigens are involved in the development of stomach, pancreatic, gallbladder, lung, kidney, breast, ovarian, and uterine cancers (6).

Preneoplastic endometrial lesions and EC have histo-blood group phenotype changes compared to normal endometrium. Changes in glycosyltransferase activity responsible for histo-blood group phenotypic changes can be detected in premalignant endometrial lesions (8). In the advanced stage, tumor cells that have lost A and B antigens may inhibit cell motility and potentially become more metastatic.

To the best of our knowledge, till date, no study has determined the ABO blood groups and Rh factors as risk factors for EC. The ABO antigens are membrane antigens present on the surface of erythrocytes and platelets; as well as on vascular, intestinal, cervical, and mammary epithelial cells; and in dissolved form in plasma, saliva, milk, urine, and feces. In addition, there are strong reactive antibodies against the antigens that are not found in the serum on the erythrocyte surface (9).

Recently, the potential roles of the ABO blood groups in the pathogenesis of certain carcinomas have been reported. However, only few studies have been conducted regarding the relationship between the ABO blood groups and gynecological carcinomas. Therefore, identifying the genetic risk factors of EC is an important area of research. There are limited studies in the literature investigating the relationship between the ABO blood groups and EC (6,10,11,12,13,14,15,16). Overall, studies have reported that the ABO blood groups are associated with significant clinicopathological parameters and survival outcomes in patients with EC and they are observed as characteristic ratios among these patients. However, the results of these studies are controversial to some extent, and many studies have reported no statistically significant correlation between the ABO blood groups and pathophysiology of EC.

This retrospective study examines the possibility of a significant relationship between blood groups and patients with EC diagnosed in the last 10 years who were without any metastasis at the time of diagnosis. Understanding whether people with a certain blood group possess a higher risk of developing EC will in turn help in gaining an insight into the carcinogenesis, prevention, and early diagnosis of EC, which are key aspects of successful treatment.

Material and Methods

The clinical and pathological data of all patients diagnosed with atypical endometrial hyperplasia or early-stage EC following probe curettage or hysterectomy in University of Health Sciences Türkiye, Ümraniye Training and Research Hospital between 2010 and 2020 were collected from the hospital automation system and retrospectively analyzed.

The frequency of detection of the ABO blood groups in the general Turkish population was compared with that of the study population. Patient data included their ABO blood groups, age at diagnosis, age at menopause, International Federation of Obstetrics and Gynecology (FIGO) stage, tumor grade, and tumor subtypes. The histological classification of EC was based on the World Health Organization classification (10). Tumors were divided into three groups according to FIGO classification as highly differentiated (grade 1),

moderately differentiated (grade 2), or undifferentiated (grade 3) (17). FIGO IA, IB, and II were evaluated as early-stage EC (18). The ABO blood groups were determined using traditional serological methods and classified as A, B, AB, and O.

Patients diagnosed with concomitant cervical cancer or synchronous tumors were excluded from the study. Women who were diagnosed with atypical endometrial hyperplasia by endometrial biopsy and had been treated with Mirena or undergone hysterectomy in another clinic were excluded from the study. Patients with pelvic radiotherapy, polycystic ovarian syndrome, Lynch 2 syndrome, breast cancer, colon cancer, and a history of esaor; or those with benign diseases, including endometrial hyperplasia without atypia; and patients with metastatic advanced stage (stages 3 and 4) EC at diagnosis were excluded from the study. Patients who had not undergone menopause at the time of the diagnosis of endometrial hyperplasia with atypia or early-stage EC were not included in the comparison analysis of the ABO blood groups with respect to menopause age.

Patients whose probe curettage or hysterectomy material was evaluated as endometrial hyperplasia with atypia and early-stage (stages 1A, 1B, 2) non-metastatic EC; patients with a history of diabetes mellitus, hypertension, hypothyroidism, and gallbladder disease; patients who were nulliparous, multiparous, and infertile; patients with a family history of EC; and patients with abnormal uterine or postmenopausal bleeding were included in the study.

After implementing the inclusion and exclusion criteria, 575 patients were reviewed and included in the final analysis. Ethical approval was obtained from the Local Ethics Committee of the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital (date: March 18, 2020; confirmation number: B.10.1.TKH.4.34.H.GP.0.01/65). Informed consent was obtained from all the participants included in this crosssectional retrospective study.

Statistical Analysis

The IBM Statistical Package for the Social Sciences Statistics 22 program was used for statistical analysis. The suitability of the parameters to the normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro-Wilks tests. While evaluating the study data, descriptive statistical methods (mean, standard deviation, frequency) and One-Way Analysis of Variance test were used to compare the normally distributed parameters to the quantitative data, and the Tukey's honest significance test was used to determine the group that caused the difference. Student's t-test was used to compare the normally distributed parameters between two groups. Chi-square test and Continuity (Yates) correction were used to compare qualitative data. Pearson correlation analysis was used to examine the relationships between parameters conforming to the normal distribution. Significance was evaluated at the $p<0.05$ level.

Results

The study included 575 women aged between 18 and 87 years at the time of diagnosis. The mean age of the patients was 55.14±11.32 years. Of the included patients, 326 (56.7%) were menopausal, and their age at menopause was 29–57 years (mean age =48.47±4.89 years). The blood groups A, O, B, and AB were present in 49.6%, 30.3%, 13%, and 7.1% patients, respectively. Of the patients, 54.4% had atypical endometrial hyperplasia and 44.9% had endometrial malignancies. In terms of EC grade, 26.8%, 17%, and 11.3% patients had grade 2, grade 1, and grade 3 EC. Of the patients, 49.9% had endometrioid adenocarcinoma and 10.6% had non-endometrioid adenocarcinoma. Mixed tumors and uterine sarcomas were observed in 8.5% and 8% of the patients, respectively (Table 1).

The blood groups B, A, and AB were most commonly observed of women with atypical endometrial hyperplasia, endometrioid adenocarcinoma or uterine sarcoma, and non-endometrioid adenocarcinoma, respectively. However, no statistically significant relationship was found among the differences in the prevalence of ABO group. The most common blood groups in patients with grades 1, 2, and 3 ECs were A, O, and B, respectively. The patient's age at diagnosis was lower in those with the blood group AB than in patients having other blood groups; however, this difference was not statistically significant. No statistically significant difference was found between the blood groups in terms of the mean age at diagnosis and menopause ($p>0.05$). There was no statistically significant difference among the blood groups in terms of the incidence of atypical endometrial hyperplasia, endometrioid adenocarcinoma and non-endometrioid adenocarcinoma, mixed tumors, and uterine sarcomas and grade distributions ($p>0.05$) (Table 2).

The mean age at menopause was lower in patients with EC than in patients without cancer, but the difference was not statistically significant. There was no statistically significant difference between the study parameters in terms of the mean age at menopause ($p>0.05$) (Table 3).

The mean age at diagnosis was significantly lower in patients with atypical endometrial hyperplasia with atypia than in patients without atypia ($p=0.000$; $p<0.05$). The mean age at diagnosis was significantly higher in patients with endometrial malignancies than that in patients without cancer ($p=0.000$; $p<0.05$). A statistically significant difference was found among tumor grades with respect to the mean age at diagnosis ($p=0.000$; $p<0.05$). The mean age

Table 1. Distribution of study parameters

		n	%
Blood type	Type A	285	49.6
	Type B	75	13.0
	Type O	174	30.3
	Type AB	41	7.1
Menopause status	Yes	326	56.7
	No	249	43.3
Atypical endometrial hyperplasia as a result of probe curettage	No	262	45.6
	Yes	313	54.4
Endometrial cancer as a result of probe curettage	No	317	55.1
	Yes	258	44.9
Grade	1	98	17.0
	2	154	26.8
	3	65	11.3
Endometrioid adenocarcinoma	No	288	50.1
	Yes	287	49.9
Non-endometrioid adenocarcinoma	No	514	89.4
	Yes	61	10.6
Mixed tumor	No	526	91.5
	Yes	49	8.5
Uterine sarcoma	No	529	92
	Yes	46	8

at diagnosis was significantly lower in patients with grade 1 tumors than in patients with grade 3 tumors (p=0.004, p<0.05). There was no significant difference among the other tumor grades (p>0.05). The mean age at diagnosis was significantly higher in patients with EC subtypes than that in patients without cancer (p=0.000; p<0.05). The mean age at diagnosis was significantly higher in patients with endometrioid adenocarcinoma, non-endometrioid adenocarcinoma, mixed tumors, and uterine sarcomas than in patients without these diseases (p=0.000; p<0.05) (Table 4).

Cancer was detected in 78% of the patients with atypical endometrial hyperplasia, among whom 10.9%, 9.9%, and 1.3% patients were diagnosed with grades 1, 2, and 3 EC, respectively (p=0.000, p<0.05). The incidence rate of endometrioid adenocarcinoma was significantly lower in patients with atypical endometrial hyperplasia (20.8%) than in patients without hyperplasia (84.7%) (p=0.000; p<0.05). The incidence rate of non-endometrioid adenocarcinoma was significantly lower in patients with atypical endometrial hyperplasia (2.2%) than in patients without hyperplasia (20.6%) (p=0.000; p<0.05). The incidence rate of mixed tumors was significantly lower in patients with atypical endometrial hyperplasia (1.6%) than in patients without hyperplasia (16.8%) (p=0.000; p<0.05). The incidence of uterine sarcoma was significantly lower in patients with atypical endometrial hyperplasia (1%) than in patients without hyperplasia (16.4%) (p=0.000; p<0.05) (Table 5).

The incidence rate of grades 1 (24%), 2 (50%), and 3 (22.1%) EC were significantly higher in patients with endometrial malignancies than in patients without malignancies (78%) (p=0.000; p<0.05). The incidence rate of endometrioid adenocarcinoma was significantly higher in patients with endometrial malignancies (88%) than in patients without malignancies (18.9%) (p=0.000; p<0.05). The incidence of non-endometrioid adenocarcinoma was significantly higher in patients with endometrial malignancies (19.4%) than in patients without malignancies (3.5%) (p=0.000; p<0.05). The incidence of mixed tumors was significantly higher in patients with endometrial malignancies (15.9%) than in patients without malignancies (2.5%) (p=0.000; p<0.05). The incidence of uterine sarcomas was significantly higher in patients with endometrial malignancies (12.8%) than in patients without malignancies (4.1%) (p=0.000; p<0.05) (Table 6).

There was a weakly positive (14.5%) but no statistically significant relationship was found between the age at diagnosis and menopause (p>0.05) (Table 7).

Table 2. Evaluations of blood group

		Type A	Type B	Type O	Type AB	
		Average ± SD	Average ± SD	Average ± SD	Average ± SD	[1]p
Age at diagnosis		55.14±11.2	55.39±10.49	55.93±11.75	51.37±11.38	0.143
Age at menopause		48.74±5.00	48.92±4.68	48.25±4.71	46.22±5.11	0.183
		n (%)	n (%)	n (%)	n (%)	[2]p
Atypical endometrial hyperplasia as a result of probe curettage	No	138 (48.4%)	31 (41.3%)	74 (42.5%)	19 (46.3%)	0.545
	Yes	147 (51.6%)	44 (58.7%)	100 (57.5%)	22 (53.7%)	
Endometrial cancer as a result of probe curettage	No	152 (53.3%)	44 (58.7%)	97 (55.7%)	24 (58.5%)	0.808
	Yes	133 (46.7%)	31 (41.3%)	77 (44.3%)	17 (41.5%)	
Grade	None	119 (41.8%)	37 (49.3%)	80 (46%)	22 (53.7%)	0.533
	1	52 (18.2%)	8 (10.7%)	31 (17.8%)	7 (17.1%)	
	2	77 (27%)	19 (25.3%)	49 (28.2%)	9 (22%)	
	3	37 (13%)	11 (14.7%)	14 (8%)	3 (7.3%)	
Endometrioid adenocarcinoma	No	130 (45.6%)	43 (57.3%)	90 (51.7%)	25 (61%)	0.112
	Yes	155 (54.4%)	32 (42.7%)	84 (48.3%)	16 (39%)	
Non-endometrioid adenocarcinoma	No	253 (88.8%)	66 (88%)	159 (91.4%)	36 (87.8%)	0.777
	Yes	32 (11.2%)	9 (12%)	15 (8.6%)	5 (12.2%)	
Mixed tumor	No	257 (90.2%)	68 (90.7%)	164 (94.3%)	37 (90.2%)	0.478
	Yes	28 (9.8%)	7 (9.3%)	10 (5.7%)	4 (9.8%)	
Uterine sarcoma	No	257 (90.2%)	68 (90.7%)	166 (95.4%)	38 (92.7%)	0.237
	Yes	28 (9.8%)	7 (9.3%)	8 (4.6%)	3 (7.3%)	

[1]One-Way ANOVA test,[2] chi-square test, SD: Standard deviation

Table 3. Evaluation of age at menopause according to study parameters

		Age at menopause	
		Average ± SD	p
Atypical endometrial hyperplasia as a result of probe curettage	No	48.18±5.04	0.192
	Yes	48.91±4.64	
Endometrial cancer as a result of probe curettage	No	49.04±4.62	0.082
	Yes	48.08±5.04	
Grade	None	49.26±4.50	[+]0.112
	1	47.35±5.26	
	2	48.30±5.16	
	3	48.69±4.39	
Endometrioid adenocarcinoma	No	48.87±4.72	0.254
	Yes	48.23±4.98	
Non-endometrioid adenocarcinoma	No	48.53±4.95	0.573
	Yes	48.10±4.55	
Mixed tumor	No	48.41±5.00	0.566
	Yes	48.89±3.94	
Uterine sarcoma	No	48.42±4.93	0.618
	Yes	48.86±4.57	

Student's t-test, [+]One-Way ANOVA test, SD: Standard deviation

Table 4. Evaluation of age at diagnosis according to study parameters

		Age at diagnosis	
		Average ± SD	p
Atypical endometrial hyperplasia as a result of probe curettage	No	59.20±10.57	0.000*
	Yes	51.74±10.81	
Endometrial cancer as a result of probe curettage	No	52.10±10.84	0.000*
	Yes	58.87±10.79	
Grade	None	51.03±10.58	⁺0.000*
	1	55.80±11.88	
	2	58.86±10.32	
	3	61.62±9.31	
Endometrioid adenocarcinoma	No	52.11±11.05	0.000*
	Yes	58.17±10.78	
Non-endometrioid adenocarcinoma	No	54.25±11.19	0.000*
	Yes	62.61±9.62	
Mixed tumor	No	54.48±11.28	0.000*
	Yes	62.22±9.15	
Uterine sarcoma	No	54.66±11.26	0.001*
	Yes	60.65±10.66	

Student's t-test, ⁺One-Way ANOVA test, *p<0.05, SD: Standard deviation

Table 5. Evaluations for the presence of atypical endometrial hyperplasia

		Atypical endometrial hyperplasia as a result of probe curettage		
		No	Yes	
		n (%)	n (%)	p
Grade	None	14 (5.3%)	244 (78%)	0.000*
	1	64 (24.4%)	34 (10.9%)	
	2	123 (46.9%)	31 (9.9%)	
	3	61 (23.3%)	4 (1.3%)	
Endometrioid adenocarcinoma	No	40 (15.3%)	248 (79.2%)	0.000*
	Yes	222 (84.7%)	65 (20.8%)	
Non-endometrioid adenocarcinoma	No	208 (79.4%)	306 (97.8%)	⁺0.000*
	Yes	54 (20.6%)	7 (2.2%)	
Mixed tumor	No	218 (83.2%)	308 (98.4%)	⁺0.000*
	Yes	44 (16.8%)	5 (1.6%)	
Uterine sarcoma	No	219 (83.6%)	310 (99%)	⁺0.000*
	Yes	43 (16.4%)	3 (1%)	

Chi-square test, ⁺Continuity (yates) correction, *p<0.05

Discussion

ABO blood groups have been associated with the risk of several malignancies. However, findings regarding gynecological malignancies are inconsistent and contradictory. ABO and Rh blood groups may differ depending on ethnicity and geography (19). The most common blood group is O in Western countries and A in Türkiye, Greece and Bulgaria (20,21).

After Aird reported that the blood group A played an important role in etiology of gastric cancer, the role of blood groups in the etiology of other cancer types gained traction as a research topic (7).

In the study by İnci and Karataş (22), the blood group distribution of all the participants was similar to that of the general population of Istanbul (A>O>B>AB) (15). Consistent with the literature, age was observed to be an important factor in the development of cancer in the current study (22). Similarly, the blood group distribution in the present study was A>O>B>AB.

Moreover, in this study, the order of blood group distribution of women with atypical endometrial hyperplasia was B>O>AB>A. The blood group A was most common among women with endometrioid adenocarcinoma or uterine sarcoma, whereas the blood group AB was most common among women with non-endometrioid adenocarcinoma; however, the difference was not statistically significant. In a study conducted by Xu et al. (6), women with EC were more likely to have the blood group A.

Various potential mechanisms have been suggested to elucidate the relationship between the ABO blood groups and cancer risk, including inflammation, intercellular adhesion, and membrane signaling.

Blood group antigens are expressed on the surface of erythrocyte and many other epithelial cells. Tumorigenesis may be affected by changes in glycosyltransferase and difference in expression of blood group antigens in epithelial cells (23). A, B, and H antigens were detected in cases of EC tumors but not in normal endometrium. H antigen is commonly detected in patients with EC (8). This result may explain the low risk of cancer in women with non-O blood type. However, it is unclear if the A and B antigens work differently in the pathogenesis of EC. A previous study suggested that there is a positive correlation

Table 6. Evaluations regarding the presence of endometrial cancer

		Endometrial cancer as a result of probe curettage		
		No	Yes	
		n (%)	n (%)	p
Grade	None	248 (78.2%)	10 (3.9%)	0.000*
	1	36 (11.4%)	62 (24.0%)	
	2	25 (7.9%)	129 (50.0%)	
	3	8 (2.5%)	57 (22.1%)	
Endometrioid adenocarcinoma	No	257 (81.1%)	31 (12.0%)	0.000*
	Yes	60 (18.9%)	227 (88.0%)	
Non-endometrioid adenocarcinoma	No	306 (96.5%)	208 (80.6%)	+0.000*
	Yes	11 (3.5%)	50 (19.4%)	
Mixed tumor	No	309 (97.5%)	217 (84.1%)	+0.000*
	Yes	8 (2.5%)	41 (15.9%)	
Uterine sarcoma	No	304 (95.9%)	225 (87.2%)	+0.000*
	Yes	13 (4.1%)	33 (12.8%)	

Chi-square test, +Continuity (yates) correction, *p<0.05

Table 7. Relationship between age at diagnosis and age at menopause

	Age at diagnosis and age at menopause
r	0.145
p	0.009*

Pearson correlation analysis, *p<0.05

between antigen A levels and the risk of cancer. The dose-response relationship suggests that antigen A has an effect on the development of EC among these women (6).

The high risk of cancer in women with blood group A seen in this study is consistent with the observations made by several previous studies (24); however, this result is inconsistent with several other studies (23) reporting that the blood group B is associated with the highest cancer risk (6).

In the present study, no significant difference was observed between the blood groups in terms of atypical endometrial hyperplasia, early-stage (1A, 1B, and 2) endometrial malignancies, grade distributions (G1, G2, and G3), endometrioid and non-endometrioid adenocarcinomas, mixed tumors, and uterine sarcomas.

In summary, the results obtained in the present study prove that there is no relationship between the ABO blood groups and subtypes, grades, and stages of EC. Our results are consistent with the results of the study by Yuzhalin and Kutikhin (10) that involved 440 patients with EC and the study by Gitas et al. (16) that involving involved 202 patients with EC. In the study conducted by İnci and Karataş (22) involving 37 women diagnosed with uterine cancer, no significant difference was found between the blood groups of the patients; however, the blood group A was more common than the other blood groups in the patients (13). The same study also reported that the blood group ARh (+) was significantly more common in patients with malignant melanoma, kidney, colorectal, breast, and ovarian cancers, whereas the blood group ORh (+) was significantly more common in patients with pancreatic cancer (22).

The results of the present study is in contradict with those of other studies reporting that the blood group A or B was associated with a lower or higher risk of EC compared with the blood group O (23,24). Most of these studies identified the blood group A or O as an independent risk factor. As these blood groups are the most common blood groups in the general population, it can lead to statistical bias.

Conversely, in a retrospective study involving 968 Italian women, Marinaccio et al. (13) reported that the incidence rate of EC was the highest in women with blood group A. However, Nakashidze et al. (11) reported that the blood group O was associated with a higher risk of EC than the other blood groups. Adamian (14) evaluated 548 Armenian women with EC and reported that women with the blood group AB exhibited a significantly higher risk of developing EC than the women with the blood group O.

According to the 6-year retrospective analysis by Akış et al. (25) involving 122 women diagnosed with early-stage endometrioid adenocarcinoma, the mean age at diagnosis was 57.3±0.9 years, which was not statistically significant. However, according to our 10-year analysis, the mean age of patients at diagnosis was 58.17±10.78 years in 287 women diagnosed with early-stage (1A, 1B, and 2) endometrioid adenocarcinoma, and a significant difference was found compared with the other EC subtypes. Furthermore, there was no significant difference in the age of patients at menopause with respect to the ABO blood groups. This result is consistent with that of Gitas et al. (16) and inconsistent with that of Yuzhalin and Kutikhin (10).

In the present study, the age at diagnosis and menopause were found to be lower in patients with the blood group AB, but the difference was not statistically significant. The mean age at diagnosis was significantly lower in patients with atypical endometrial hyperplasia than in patients without atypia. The mean age at diagnosis was significantly higher in patients with endometrial malignancies than in patients without malignancies. In all the patients with EC subtypes, the mean age at diagnosis was higher and found to be significant. However, no significant difference was found between the ABO blood groups and the mean age at diagnosis and menopause. However, a weakly positive significant correlation was found between the age at diagnosis and menopause.

In the study by Mohammadian et al. (15), EC was reported as the most common histological type; 135 people (77.1%) had early-stage (I and II) cancer. Serous papillary variants were detected in 10.3%, carcinosarcoma in 5.7%, and clear cell major histological variants were detected in 5.1% of the patients. Overall, 48.2% of the patients were grade 1, 21.8% were grade 2, and 30% were grade 3. The frequencies of the A, B, AB, and O blood groups were 37%, 20.8%, 12.1%, and 30.1%, respectively. When the authors classified the ABO blood groups as A vs. non-A, a significant relationship between the A antigen and the clinicopathological results and EC grade was observed (15).

Similarly, in this study, the incidence rate of endometrioid adenocarcinoma was 88% in patients with endometrial malignancies, which was the most common subtype. Furthermore, the patient population (n=575) comprised early-stage (I and II) patients. In the present study, the blood groups A, O, B, and AB were exhibited by 49.6%, 30.3%, 13%, and 7.1% patients, respectively. Atypical endometrial hyperplasia and endometrial malignancies were detected in 54.4% and 44.9% patients, respectively. In terms of grade, 26.8%, 17%, and 11.3% patients were diagnosed with grades 2, 1, and 3 EC. Overall, 49.9% patients had endometrioid adenocarcinoma, 10.6% had non-endometrioid adenocarcinoma, 8.5% had mixed tumors, and 8% had uterine sarcomas. In contrast to a previous study conducted in Iran (20) (n=175), the patients were not divided into two groups (A vs. non-A) like in the present study, and the sample size was considerably larger (n=575).

In the present study, the blood group A was the most common blood group in patients with EC. This finding is consistent with that of other studies conducted in Siberia (10), China (6), Italy (12,13), and Iran (15). However, these findings are inconsistent with studies conducted in Georgia and Saudi Arabia where the blood group O was reportedly predominant in patients with EC (11,18). In two separate studies conducted in Italy and Iran, patients with the blood group A exhibited a lower risk of developing grade 3 EC (12,15). In the present study, the blood group A was most commonly seen in patients with grade 1 EC, whereas blood group O and B was the most common in patients with grades 2 and 3 EC, respectively. However, these differences were not statistically significant.

An advantage of the present study is that the follow-up data are well documented electronically.

This is the first study conducted in Türkiye where ABO antigens were investigated as diagnostic markers for early-stage EC and its subtypes.

The findings of this study revealed that the clinical parameters of early-stage EC are not dependent on the prevalence of the ABO blood groups. Hence, it can be concluded that blood group screening is probably not an early biomarker for early-stage EC. The limited but very heterogeneous results reported in the literature suggest that the ABO blood groups may not be a key factor in endometrial carcinogenesis.

The findings of the present study support the hypothesis that the ABO blood groups cannot help in the detection of early-stage EC.

Study Limitations

First, data regarding lifestyle changes, genetic and environmental factors of patients with early-stage EC could not be obtained; therefore, the contribution of these factors to cancer development could not be evaluated. Therefore, the future studies should evaluate all results considering that the results may vary according to the presence of other factors that have an effect on cancer development. Second, the relatively small number of cases in our cohort did not allow us to reach definitive conclusions regarding the possible interactions between the ABO blood groups and risk of EC. This warrants for future multicenter studies with larger patient groups evaluating a more comprehensive data set to improve the early detection of EC, which is crucial for its successful treatment. Furthermore, the retrospective design of the study can be considered a limitation. However, a prospective analysis could not have provided better documentation than a retrospective analysis.

Hence, there is an urgent need for detailed molecular and genetic studies regarding the role of blood groups in the etiopathogenesis of cancer.

In addition, since only the medical records of the patients were analyzed, we were unable to evaluate the role of various potential confounders such as smoking status, use of oral contraceptives, and duration of breastfeeding.

Conclusion

ABO blood groups have the potential to be an easy-to-access, inexpensive biomarker for EC prevention, early detection, and routine use in screening programs; however, our results confirmed the limited diagnostic value of blood groups for EC. Therefore, blood group screening is less effective in diagnosing early-stage EC than the current gold standard. Nevertheless, we hope that this study encourages further research on this topic.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Local Ethics Committee of the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital (date: March 18, 2020; confirmation number: B.10.1.TKH.4.34.H.GP.0.01/65).

Informed Consent: Informed consent was obtained from all the participants included in this crosssectional retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.M.P., Concept: R.M.P., H.İ.E., Design: R.M.P., H.İ.E., Y.Ş., Data Collection or Processing: R.M.P., Y.Ş., Analysis or Interpretation: R.M.P., H.İ.E., Literature Search: R.M.P., H.İ.E., Y.Ş., Writing: R.M.P., H.İ.E.

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References

1. Epidemiology of Endometrial Cancer Consortium (E2C2). Available from: https://epi.grants.cancer.gov/eecc/ (Accessed on: October 10, 2019). [Crossref]
2. Gultekin M, Kucukyildiz I, Karaca MZ, Dundar S, Boztas G, Turan SH, et al. Trends of Gynecological Cancers in Turkey: Toward Europe or Asia?. Int J Gynecol Cancer. 2017;27(8S Suppl 1):1525-1533. [Crossref]
3. Arvas MM, Tokgözoğlu N. Management of Early Stage Endometrial Cancer, Turkiye Klinikleri J Gynecol Obst-Special Topics. 2014;7:59-66. [Crossref]
4. Lachance JA, Everett EN, Greer B, Mandel L, Swisher E, Tamimi H, et al. The effect of age on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecol Oncol. 2006;101:470-475. [Crossref]
5. Batıoğlu S, Songül S, Keleş G, Durmuş Z. Ortalama menopoz yaşı. Dr. Z.T.B. Kadın Hastanesi Kadın Doğum Dergisi. 1990;2:19-22. [Crossref]

6. Xu WH, Zheng W, Xiang YB, Shu XO. ABO blood type is associated with endometrial cancer risk in Chinese women. Chin J Cancer. 2011;30:766-771. [Crossref]
7. Huang JY, Wang R, Gao YT, Yuan JM. ABO blood type and the risk of cancer - Findings from the Shanghai Cohort Study. PLoS One. 2017;12:e0184295. [Crossref]
8. Skovlund VR. ABH and related histo-blood group antigens in normal & malignant human endometrium in relation to genetic and hormonal factors. APMIS Suppl. 1997;69:1-33. [Crossref]
9. Bilgen H. Kan grup antijenleri. İ.Ü. Cerrahpaşa Tıp Fakültesi Sürekli Tıp Eğitimi Etkinlikleri Herkes için Transfüzyon Tıbbı Sempozyum Dizisi No: 44: 2005;45-65. [Crossref]
10. Yuzhalin AE, Kutikhin AG. ABO and Rh blood groups in relation to ovarian, endometrial and cervical cancer risk among the population of South-East Siberia. Asian Pac J Cancer Prev. 2012;13:5091-5096. [Crossref]
11. Nakashidze I, Diasamidze A, Kotrikadze N, Nagervadze M. Distribution of erythrocyte phenotypic groups in women with benign tumors of the uterus in Adjara Oncology Centre. Georgian Med News. 2012;15-18. [Crossref]
12. Mandato VD, Torricelli F, Mastrofilippo V, Ciarlini G, Pirillo D, Farnetti E, et al. Prognostic impact of ABO blood group on type I endometrial cancer patients- results from our own and other studies. J Cancer. 2017;8:2828-2835. [Crossref]
13. Marinaccio M, Traversa A, Carioggia E, Valentino L, Coviello M, Salamanna S, et al. [Blood groups of the ABO system and survival rate in gynecologic tumors]. Minerva Ginecol. 1995;47:69-76. [Crossref]
14. Adamian RT. [Blood-type and rhesus distribution in Armenian women with endometrial carcinoma]. Vopr Onkol. 2005,51:575-576. [Crossref]
15. Mohammadian S, Pouresmaeili F, Mohammadian A. Prognostic impact of ABO blood group on type I endometrial cancer in a population of Iranian patients. Hum Antibodies. 2020;28:313-317. [Crossref]
16. Gitas G, Proppe L, Alkatout I, Tsolakidis D, Rody A, Kotanidis C, et al. Is ABO blood group a risk or prognostic factor for patients with endometrioid endometrial cancer? A retrospective analysis in Germany. Blood Transfus. 2020;18:465-470. [Crossref]
17. Abu-Rustum NR, Zhou Q, Iasonos A, Alektiar KM, Leitao MM Jr, Chi DS, et al. The revised 2009 FIGO staging system for endometrial cancer: should the 1988 FIGO stages IA and IB be altered?. Int J Gynecol Cancer. 2011;21:511-516. [Crossref]
18. Abu-Zaid A, Alsabban M, Abuzaid M, AlOmar O, Salem H, Al-Badawi IA. Preoperative thrombocytosis as a prognostic factor in endometrioid-type endometrial carcinoma. Ann Saudi Med. 2017;37:393-400. [Crossref]
19. Guyton AC, Hall JE. Blood Types; Transfusion; Tissue and Organ Transplantation. In: Guyton AC, Hall JE, editors. Textbook of Medical Physiology. Philedelphia: W.B. Saunders; 2006:452-53.
20. Eren C. Analysis of Distribution of ABO and Rh Blood Groups in İstanbul Province. Dicle Med J. 2019;46.[Crossref]
21. Garatty G, Glynn SA, Mc Entire R; Retrovirus Epidemiology Donor Study. ABO and Rh(D) phenotype frequencies of different racial/ethnic groups in the United States. Transfusion. 2004;44:703-706. [Crossref]
22. İnci F, Karataş F. Kanser hastalarında ABO ve rhesus kan gruplarının dağılımı. Uludağ Üniversitesi Tıp Fakültesi Dergisi. 2020;46:379-384. [Crossref]
23. Wolpin BM, Chan AT, Hartge P, Chanock SJ, Kraft P, Hunter DJ, et al. ABO blood group and the risk of pancreatic cancer. J Natl Cancer Inst. 2009;101:424-431. [Crossref]
24. Henderson J, Seagroatt V, Goldacre M. Ovarian cancer and ABO blood groups. J Epidemiol Community Health. 1993;47:287-289. [Crossref]
25. Akış S, Kabaca C, Keleş E, Öztürk UK, Özyürek E, Api M, et al. Tumor diameter as a predictor of lymph node involvement in endometrioid type endometrial adenocarcinomas. J Obstet Gynaecol Res. 2021;47:3968-3978. [Crossref]